

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference W2170-000000	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. PCT/JP2005/006408	International filing date ( <i>day/month/year</i> ) 25 March 2005 (25.03.2005)	Priority date ( <i>day/month/year</i> ) 25 March 2004 (25.03.2004)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant OTSUKA PHARMACEUTICAL CO., LTD.			

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 6 sheets, including this cover sheet.  In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

<p style="text-align: center;">The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 338 82 70</p>	<p>Date of issuance of this report 26 September 2006 (26.09.2006)</p> <p>Authorized officer  Yoshiko Kuwahara</p> <p>e-mail: pt07@wipo.int</p>
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# PATENT COOPERATION TREATY

REC'D 30 MAY 2005

WIPO

PCT

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/JP2005/006408

International filing date (day/month/year)  
25.03.2005

Priority date (day/month/year)  
25.03.2004

International Patent Classification (IPC) or both national classification and IPC  
C07C213/02, C07D295/08, C07D211/46, C07C215/82, C07C215/76

Applicant  
OTSUKA PHARMACEUTICAL CO., LTD.

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk - Pays Bas  
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Fitz, W

Telephone No. +31 70 340-4359



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/JP2005/006408

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material:  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing:  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/JP2005/006408

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**Box No. V Reasoned statement under Rule 43*b*/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-12
	No: Claims	-
Inventive step (IS)	Yes: Claims	1-12
	No: Claims	-
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	-

**2. Citations and explanations**

**see separate sheet**

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**Box No. VIII Certain observations on the International application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Item V.**

D1: HAGA, KAZUO ET AL: BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, 59(3), 803 -7 CODEN: BCSJA8; ISSN: 0009-2673, 1986, XP008047270

D2: LEONARD, NELSON J. ET AL: JOURNAL OF ORGANIC CHEMISTRY, 21, 1187-8 CODEN: JOCEAH; ISSN: 0022-3263, 1956, XP008047221

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and shows condensation reactions of 1,4-cyclohexanediones and secondary aromatic amines in the presence of p-toluenesulfonic acid. While most diarylamines are converted into the triarylamine, the nitrosubstituted diarylamines also yield a second product, namely the aminophenol compounds (cf. page 803, Table 1, compounds 4j-l) in yields ranging from 7-12%.

The subject-matter of claim 1 differs from this known process in that the condensation reaction is performed under neutral or basic conditions.

Accordingly, the subject-matter of claim 1 (and dependent claims 2-12) is new (Article 33(2) PCT).

The present process (run under neutral or basic conditions, yields from 27-89% in examples 1-10) has the advantage that the aminophenol can be obtained in better yield as compared to the process of D1 (run under acidic conditions, yields ranging from 0-12%).

The problem to be solved by the present invention may be regarded as the provision of an improved process for the preparation of aminophenols starting from cyclohexanediones and amines.

D1, alone or in combination with another document, does not suggest that the yield could be improved by running the reaction at neutral or basic conditions.

Accordingly, the subject-matter of claim 1 (and dependent claims 2-12) is considered as involving an inventive step (Article 33(3) PCT).

**Item VIII.**

1.) It is clear from the description on page 22, lines 24-27 and from the examples that the cyclohexanedione compound of the formula (2) should be used in an equimolar amount to 10 mole based on 1 mole of the amine of the formula (3), in order to obtain the desired

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/JP2005/006408

aminophenol product.

D2 confirms the importance of the amount of the cyclohexanedione compound, since this document shows that when 1,4-cyclohexanedione is reacted with a molar excess of pyrrolidine or piperidine, not the aminophenol but a different product (namely the bisenamine/diaminobenzene) is obtained.

The claims should be commensurate with the disclosure and contain all essential technical features, Article 6 PCT.

2.) The term 'lower' which is used throughout the claims in connection with alkyl and alkoxy groups and the like is vague and blurs the scope of the claims, Article 6 PCT.

3.) The brackets which are used throughout the claims for the definition of the substituents of the general formulae are superfluous and give rise to a lack of clarity, Article 6 PCT.